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Interchangeability of Quinvaxem during primary vaccination schedules: Results from a phase IV, single-blind, randomized, controlled, single-center, non-inferiority study

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ABSTRACT

Combination vaccines against diphtheria, tetanus and pertussis (DTP) represent the core of childhood vaccination programs. Quinvaxem, a fully-liquid, pentavalent combination vaccine containing inactivated hepatitis B (HepB), *Haemophilus influenzae* type b (Hib) and whole-cell pertussis (wP) antigens, and tetanus and diphtheria toxoids, has been shown to be suitable for boosting children primed in infancy with another DTwP–HepB–Hib vaccine. This single-blind, randomized, controlled study was designed to demonstrate non-inferiority of a primary vaccination course (6–10–14 week schedule) of Tritanrix HB + Hib (first dose) and Quinvaxem (second/third doses) versus three doses of Quinvaxem with respect to the seroprotection/seroconversion rates for all antigens one month after vaccination course completion. Four hundred healthy subjects eligible for the local Expanded Program on Immunization were enrolled and equally randomized to the two treatment regimens. All subjects achieved seroprotection for tetanus and Hib, all except one for diphtheria, and all except two achieved seroconversion against *Bordetella pertussis*. Seroprotection against hepatitis B was achieved by 97.4% of Tritanrix HB + Hib followed by Quinvaxem and 94.9% of Quinvaxem subjects. Therefore, one month after vaccination course completion, seroprotection rates (seroconversion rate for *B. pertussis*) of Tritanrix HB + Hib followed by Quinvaxem were non-inferior to those elicited by Quinvaxem only, thus meeting the primary objective. Adverse events were comparable between the groups and were in line with the safety profile of the vaccines. The switch of vaccine had no apparent effect on safety endpoints. Our results support the use of Quinvaxem interchangeably with Tritanrix HB + Hib in a primary vaccination course and provides further evidence for the interchangeability of pentavalent vaccines (Clinical Trials.gov registry: NCT01357720).

1. Introduction

Combination vaccines against diphtheria, tetanus and pertussis (DTP) represent the core of global childhood vaccination programs. The introduction of hepatitis B (HepB) virus and *Haemophilus influenzae* type b (Hib) vaccinations into the Expanded Program on Immunization (EPI) in the 1990s has ensured that >70% of the targeted population receives the necessary vaccines [1]; yet, in 2009 over 23 million children worldwide still did not receive all three DTP doses [2], and vaccine coverage for HepB and Hib was at suboptimal levels in many countries.

Pediatric combination vaccines that include DTP with other antigens (HepB surface antigen [HBsAg] and Hib) simplify immunization delivery providing multiple advantages to children, parents, and health care providers by reducing the number of injections, clinical visits, and logistic requirements [3]. Currently six pentavalent vaccines are pre-qualified by the WHO and in use in the EPI: liquid Quinvaxem (Berna Biotech Korea Corporation), liquid Pentavac™ (Serum Institute of India Ltd.), liquid DTwP–HepB–Hib (Biological E Limited), lyophilized DTwP–HepB/Hib (Biological E Limited), Euforvac-Hib™ (LG Life Sciences) and lyophilized Tritanrix HB + Hiberix (GlaxoSmithKline Biologicals).

Although aP vaccines, developed in the 1980s, have gradually become the dominant type in the industrialized world, wP vaccines are still the most commonly used pertussis vaccines among

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the global population [4]. The higher development and production costs of aP vaccines, resulting in higher prices per dose, have outweighed their improved tolerability profile making wP vaccines still the first choice in most developing countries [5].

The United Nations Children's Fund (UNICEF) supplies vaccines to 58% of the world's children [6]. UNICEF aims to guarantee vaccine supply [7] in the event of a vaccine shortage to allow continuation of immunization programs; alternative suppliers may be sought, or vaccine deliveries may be prioritized. If alternate vaccines are supplied to a country it is theoretically possible that switching between vaccines from different manufacturers occurs. Such situations are more likely to occur when there are a limited number of suppliers, and at present the number of suppliers of WHO pre-qualified pentavalent vaccines is limited to five [8]. In 2012, UNICEF procured both fully liquid and lyophilized pentavalent vaccines in different presentations from all four manufacturers, however in 2006 and 2007 pentavalent vaccines were available from only two manufacturers [9]. It is therefore unrealistic to assume that the same vaccine will always be available for each child [10].

Few guidelines are available on vaccine interchangeability [11,12]. The WHO recommends that the same wP vaccine should be given throughout a primary vaccination course [5], but have adopted the position that if the previous type of vaccine is unknown or unavailable, any wP-containing vaccine (or aP-containing vaccine) may be used for subsequent doses [5]. It is clear that the interchangeability of prequalified wP vaccines is poorly studied; it has to our knowledge only been studied with respect to the interchangeability of a lyophilized DTwP–HBV/Hib vaccine in a primary course with a fully-liquid DTwP–HBV–Hib vaccine (Quinvaxem) as a booster [13]. This demonstrated that Quinvaxem can be used for boosting children primed in infancy with another DTwP–HepB–Hib vaccine. Currently no data are available on wP-containing pentavalent vaccine interchangeability within a primary vaccine course. Our study was designed to answer this question with respect to the two wP containing pentavalent vaccines: Quinvaxem and Tritanrix HB + Hiberix.

The primary objective was to show the non-inferiority of a primary vaccination course consisting of one dose of Tritanrix HB + Hiberix (Tritanrix HB + Hib) followed by Quinvaxem as the second and third dose versus three doses of Quinvaxem with respect to the seroprotection/seroconversion rates for all antibodies one month after completion of a 6–10–14 week vaccination course. Safety was also evaluated.

2. Materials and methods

This phase IV, single-blind (observer-blinded), randomized, comparator-controlled study was conducted at the Research Institute for Tropical Medicine (RITM), Muntinlupa City, Philippines between 30 May 2011 and 30 September 2011. Prior to commencement, the Philippines Food and Drug Administration (PFDA), and the Institutional Review Board of the RITM approved the study, which was performed in accordance with the Declaration of Helsinki and Good Clinical Practice standards. This study was registered under ClinicalTrials.gov NCT01357720. Parents/legal guardians gave written informed consent for all participants. Healthy children aged 42–62 weeks with a birth dose of HepB vaccination were included. Exclusion criteria included: treatment with an investigational medicinal product or parenteral immunoglobulins/blood products (since birth), planned administration of a vaccine not in the study protocol, immunodeficiency/immunosuppressive therapy, previous Hib/DTP vaccination, history of anaphylaxis/serious vaccine reaction, allergy to vaccine components, or participation in another clinical study.

After screening, children were randomized sequentially 1:1 to receive either one 0.5 mL dose of Tritanrix HB + Hib followed by two 0.5 mL doses of Quinvaxem (Tritanrix HB + Hib + Quinvaxem group) or three 0.5 mL doses of Quinvaxem (Quinvaxem only group), according to a randomization schedule using sealed envelopes. Vaccine preparation and administration were performed by independent personnel to maintain observer blinding (investigator).

Tritanrix HB + Hib was composed of Hiberix (lot number: A72CA647B) reconstituted using a liquid suspension of Tritanrix HB (lot number: AT15B656BD, both GlaxoSmithKline Biologicals). After reconstitution, a 0.5 mL dose contained ≥30 IU diphtheria toxoid, ≥60 IU tetanus toxoid, ≥4 IU inactivated *Bordetella pertussis*, 10 μg Hib polysaccharide conjugated to tetanus toxoid (~25 μg) as a carrier, and 10 μg HBsAg. Each 0.5 mL dose of Quinvaxem (lot number: 0451523, Berna Biotech Korea Corporation) contained ≥30 IU diphtheria toxoid, ≥60 IU tetanus toxoid, ≥4 IU inactivated *B. pertussis*, 10 μg Hib polysaccharide conjugated to CRM_{197} protein (~25 μg), and 10 μg HBsAg. Study vaccines were administered intramuscularly into the anterolateral thigh using a tuberculin syringe (length 16 mm) according to the local 6–10–14-week EPI schedule (visits 1–3, respectively).

2.1. Immunogenicity evaluation

For immunogenicity assessments 3 mL blood was taken at visit 1 (before the first dose) and visit 4 (one month after the third dose). In-house assays were used for all antigens. Anti-HepB antibodies were measured by Novartis Vaccines and Diagnostics, Marburg, Germany using an indirect ELISA with seroprotection defined as a concentration of HepB antibodies ≥10 IU/mL. The University of Rochester, New York, USA used a competitive ELISA to measure antibodies against Hib PRP with seroprotection rates defined by the two cut-off levels of ≥0.15 μg/mL and ≥1.0 μg/mL, and an indirect ELISA for diphtheria and tetanus antibodies with seroprotection defined as a concentration of ≥0.1 IU/mL. *B. pertussis* antibodies were analyzed using a whole cell ELISA at the University of Turku, Finland. As there is no definition of seroprotection for *B. pertussis*, seroconversion was defined as either concentrations ≥20 EU/mL or a ≥4-fold increase from pre-vaccination levels.

Primary endpoints at visit 4 were the percentage of subjects achieving the immunogenicity parameters defined above, with the exception of PRP at the higher cut-off level of ≥1.0 μg/mL, which was a secondary endpoint.

2.2. Safety evaluation

Solicited local (tenderness, erythema, and induration) and systemic (fever ≥38 °C) AEs after each vaccination were documented by parents/legal guardians for five days (starting on the day of vaccination) in a subject diary, together with any unsolicited AE. At each study visit the investigator asked a non-leading question to collect unsolicited AEs. Reported SAEs were recorded for up to 6 months after the final vaccination. AEs were graded as mild, moderate or severe. Whilst blinded to study vaccine, the investigator determined the possible cause of any AE and any potential relationship to study vaccine administration.

2.3. Statistical analysis

Assuming a seroprotection/seroconversion rate for each antigen of 95% in each group and a clinically significant non-inferiority limit of −10%, a sample size of 360 evaluable subjects was required to demonstrate, with an overall power of >90% and a 1-sided significance level of 2.5%, the non-inferiority of Quinvaxem given interchangeability with Tritanrix HB + Hib. Assuming a dropout rate

of approximately 10%, a sample size of 400 subjects (200 in each group) was set.

The primary and secondary analyses were performed with both the according-to-protocol (ATP) and intention-to-treat (ITT) populations. Descriptive safety analyses were performed on all subjects who received at least 1 injection of study vaccine (safety population).

The study hypothesis is as follows:

- *Null hypothesis*: The seroprotection/seroconversion rate for at least 1 antigen 1 month after 1 dose of Tritanrix HB + Hib followed by Quinvaxem as the 2nd and 3rd dose is inferior to the seroprotection/seroconversion rate 1 month after 3 vaccinations with Quinvaxem by more than −10%.
- *Alternative hypothesis*: The seroprotection/seroconversion rate for all antigens 1 month after 1 dose of Tritanrix HB + Hib followed by Quinvaxem as the 2nd and 3rd dose is not inferior to the seroprotection/seroconversion rate 1 month after 3 vaccinations with Quinvaxem by more than 10%.

The non-inferiority of Quinvaxem given interchangeably with Tritanrix HB + Hib compared with a full vaccination course of Quinvaxem would be demonstrated if the lower limit of all two-sided 95% confidence intervals (CIs; Newcombe–Wilson score method without continuity correction) of the difference in seroprotection/seroconversion rates between the two groups were simultaneously greater than −10%. If non-inferiority was demonstrated, the two-sided Fisher's exact test was performed.

3. Results

3.1. Study population

Fig. 1 shows the patient disposition. A total of 402 subjects were screened, and 400 subjects randomized equally to both groups (two subjects did not meet all inclusion/exclusion criteria). Altogether, 396 subjects (99.0%) received all three vaccinations. The mean age was 6.7 (Tritanrix HB + Hib + Quinvaxem group) and 6.8 weeks (Quinvaxem only group). Table 1 presents other demographic data.

3.2. Immunogenicity data

Immunogenicity results for the ATP population are given (ITT population results were similar). At baseline, the majority of subjects were seroprotected at the lower cut off level of ≥0.15 μg/mL in both treatment groups for Hib (Tritanrix™ HB + Hib + Quinvaxem 83.8% and Quinvaxem 84.8%). For tetanus toxoid, 88.7% of Tritanrix HB + Hib + Quinvaxem subjects and 91.9% of Quinvaxem subjects were seroprotected at baseline. For HepB almost one-third of subjects were seroprotected at baseline (Tritanrix™ HB + Hib + Quinvaxem 27.3% and Quinvaxem 30.8%), and for diphtheria less than one-fifth of subjects were seroprotected (Tritanrix HB + Hib + Quinvaxem 17% and Quinvaxem 16.7%).

One month after the third dose of vaccine, all subjects had achieved seroprotection for tetanus and Hib (100% for both antigens for both treatment groups), all except one for diphtheria (100% for Tritanrix HB + Hib + Quinvaxem and 99.5% for Quinvaxem), and all achieved seroconversion against *B. pertussis* except for two subjects (100% for Tritanrix HB + Hib + Quinvaxem and 99% for Quinvaxem). Seroprotection against hepatitis B was achieved in 97.4% of Tritanrix HB + Hib + Quinvaxem and 94.9% of Quinvaxem subjects (Fig. 2).

The non-inferiority of Quinvaxem given interchangeably with Tritanrix HB + Hib compared with a full vaccination course of Quinvaxem was demonstrated. For all individual antigens, the lower limits of the two-sided CIs of the differences in seroprotection/seroconversion rates between the two groups were all greater than −10% (Fig. 3).

3.3. Safety data

For both groups, fewer solicited local AEs were reported after the third vaccination than after the first or second (Fig. 4). Tenderness (injection site pain) was the most common local solicited AE, but was experienced by more subjects in the Tritanrix HB + Hib + Quinvaxem group after the first (64.0% vs. 54.0%), second (62.1% vs. 54.3%) and third (44.2% vs. 38.2%) vaccinations than in the Quinvaxem only group. The majority of solicited local AEs were of mild to moderate severity. After the first vaccination, more subjects who had received Tritanrix HB + Hib reported severe local AEs than subjects who had received Quinvaxem (6 vs. 3 subjects). The incidence of fever (solicited systemic AE) (Fig. 4) was lower after the third vaccination compared to the first or second vaccination in both groups. The majority of cases of fever resolved within one day of onset. The incidences of unsolicited AEs after individual vaccinations were similar in both groups ranging from 14.0% to 19.8% in the Tritanrix HB + Hib + Quinvaxem and from 12.0% to 19.6% in the Quinvaxem only group. Upper respiratory tract infections were most frequently reported; most unsolicited AEs were of mild severity.

Two subjects, both in the Tritanrix HB + Hib + Quinvaxem group, experienced SAEs: one subject died (severe respiratory failure secondary to severe pneumonia secondary to severe viral encephalitis starting one week after the third Quinvaxem vaccination), the other was withdrawn from the study (idiopathic thrompocytopoenic purpura developing 12 days after vaccination with Tritanrix HB + Hib). All SAEs were considered unrelated to the study vaccines.

4. Discussion

This study provides scientific evidence on the interchangeability of wP pentavalent vaccines in a primary vaccination course in infants according to a 6–10–14 week schedule. Our most important finding is that Quinvaxem given interchangeably with Tritanrix HB + Hib was shown to be non-inferior to a full vaccination course of Quinvaxem. Seroprotection rates for all antigens and seroconversion rates for pertussis were high, with most if not all subjects achieving seroprotection or seroconversion one month after the third vaccination, irrespective of the vaccination group.

Immune responses observed in our study to Tritanrix™ HB + Hib + Quinvaxem were comparable to responses seen in previous studies with Tritanrix™ HB + Hib only [14,15] or Quinvaxem only regimens [3]. In our study, a high percentage of infants (88.7–91.9%) were seroprotected at baseline against tetanus. In 1999, the Maternal and Neonatal Tetanus (MNT) Elimination Initiative was jointly set up by the WHO and UNICEF, aiming to eliminate MNT in those countries which had not yet done so [16]. The Philippines has an active maternal tetanus immunization program, and although MNT has not yet been eliminated, the percentage coverage of protection at birth against neonatal tetanus has increased over the last years from 22% in 2009 to 39% in 2011 [17]. The high percentage of seroprotection against tetanus observed in infants included in our study is possibly attributable to this. Additionally, the baseline seroprotection rate against Hib was also high, at 83.0–84.8%. This is in line with data reported in the literature. In one study with Tritanrix™ HB + Hib in Filipino infants, Hib seroprotection rates of 64.5–65.3% were reported [14]. Furthermore, Ortega-Barrìa et al. [18] report on the results of four phase III studies using a novel pentavalent combination vaccine compared with Tritanrix™ HB + Hib conducted in Panama/Nicaragua, Turkey, Belgium and the Philippines. The baseline seroprotection

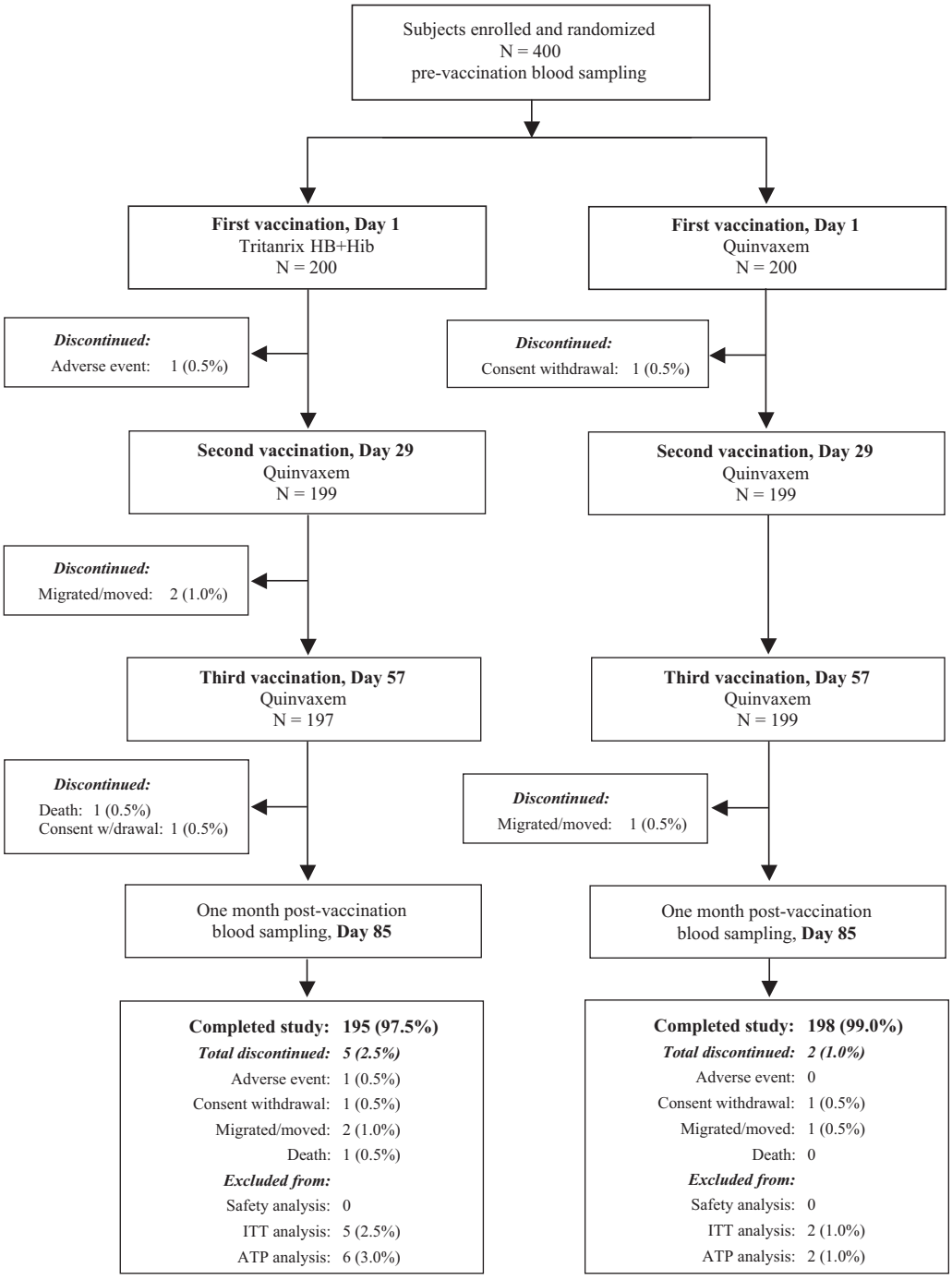

Fig. 1. Patient disposition. ATP = according-to-protocol; ITT = intention-to-treat; *N* = number of subjects in specified category.

Table 1
Baseline demographic data (safety population).

		Tritanrix™ HB + Hib + Quinvaxem *N* = 200	Quinvaxem only *N* = 200	Total *N* = 400
Sex (*n*, %)	Female	95 (47.5%)	99 (49.5%)	194 (48.5%)
	Male	105 (52.5%)	101 (50.5%)	206 (51.5%)
Age (weeks)	Median (min, max)	6 (6, 9)	7 (6, 9)	6 (6, 9)
	Mean ± SD	6.7 (0.86)	6.8 (0.91)	6.7 (0.89)
Weight (kg)	Median (min, max)	4.5 (3.1, 6.2)	4.5 (3.1, 6.0)	4.5 (3.1, 6.2)
Height (cm)	Median (min, max)	55 (50, 61)	55 (50, 62)	55 (50, 62)
BMI (kg/m^2)	Median (min, max)	14.9 (10.2, 18.8)	15.2 (10.2, 20.3)	15.1 (10.2, 20.3)

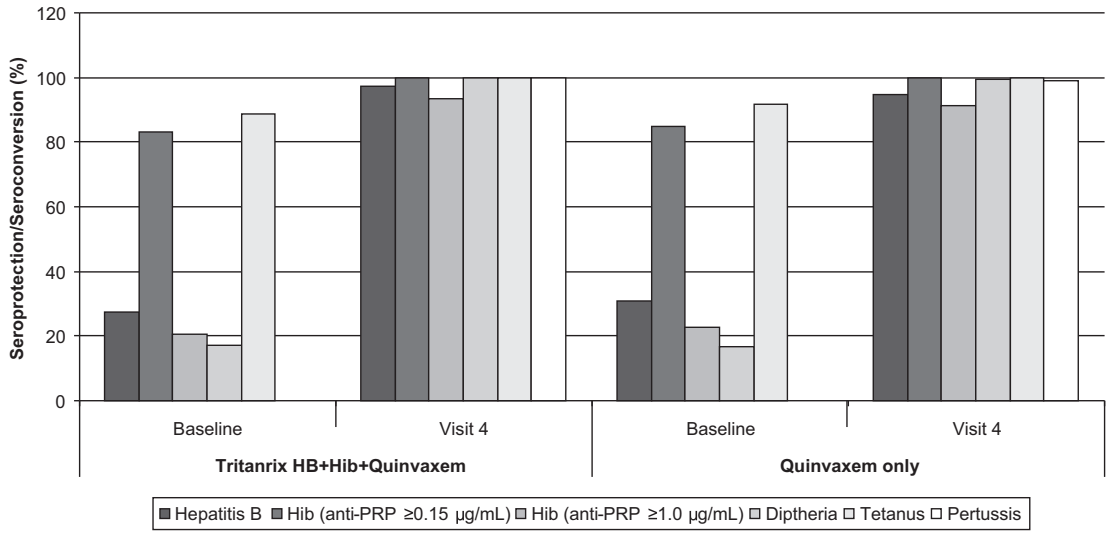

Fig. 2. Seroprotection/seroconversion rates (seroconversion rate for pertussis only) of Tritanrix HB + Hib followed by Quinvaxem and Quinvaxem only at baseline and visit 4 (one month after the third vaccination).

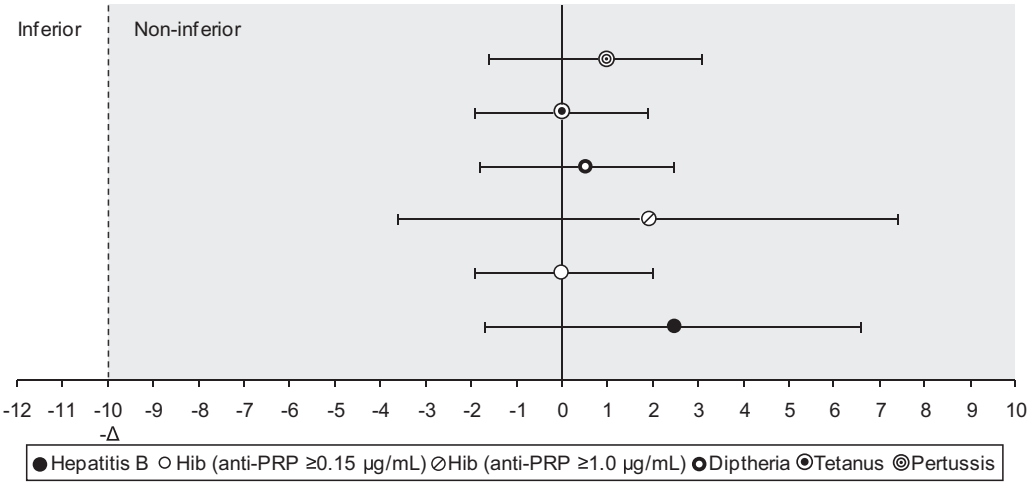

Fig. 3. Treatment difference for seroprotection/seroconversion shows that Tritanrix HB + Hib followed by Quinvaxem is non-inferior to Quinvaxem only. Hib: *H. influenzae* type b. −Δ: margin of non-inferiority. Error bars indicate 2-sided 95% confidence intervals. All values are non-significant based on two-sided Fisher's exact test.

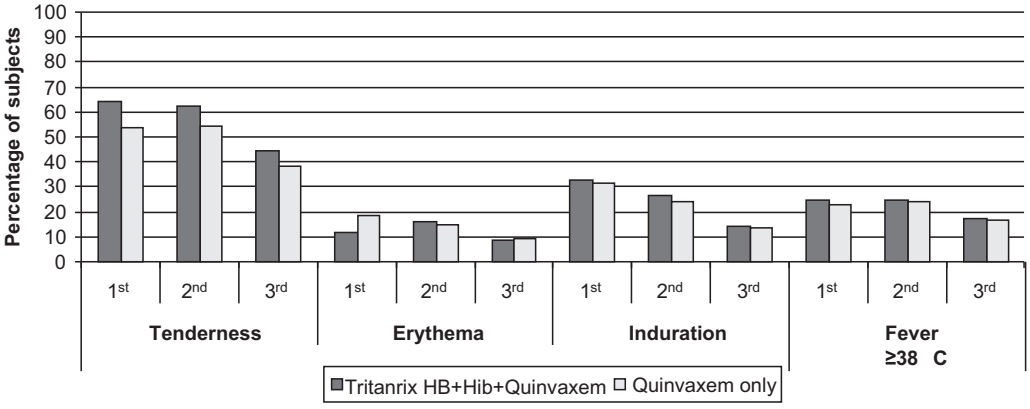

Fig. 4. Solicited local and systemic adverse events after the first, second and third vaccinations for Tritanrix HB + Hib followed by Quinvaxem and Quinvaxem only. Fever: body temperature ≥38 °C.

rates against Hib were 62.4–63.6% in the Philippines – much higher than values reported in the other countries (19.6–47.1%). However, no explanation for these high levels was provided.

Our results also show that switching from Tritanrix HB + Hib to Quinvaxem had no negative impact with regards to safety; AE patterns were comparable between the groups and well in line with those observed in earlier studies with Quinvaxem [3].

The current study was conducted to provide data on the interchangeability of wP pentavalent vaccines in a primary vaccination course. Until now, only the interchangeability of wP pentavalent vaccines as a booster has been studied [13]. Substituting a booster dose of a lyophilized pentavalent vaccine with that of a fully liquid one was shown to be highly immunogenic with a favorable safety profile. It is, however, clear that there is limited interchangeability data available. The interchangeability of the individual components of pentavalent vaccines, as well as for aP-containing vaccines has been shown [11,12,19–24]. Although data for aP containing vaccines is limited, their interchangeability is supported by the Advisory Committee on Immunization Practices (ACIP) in the USA [25] and the Public Health Agency of Canada (PHAC) [26]. The recommendations given by ACIP and the PHAC were put in place because both the USA and Canada use pentavalent vaccines from more than one manufacturer, and it is possible that different products may be used in one individual during a vaccination course as a result, for example, of migration or vaccine shortages. It has also been shown that in a vaccine shortage situation 25% of children whose vaccination was deferred did not return for the indicated vaccine [26], leaving a population of children partially vaccinated and susceptible to disease.

A reason for the limited published data may be attributable to the fact that interchangeability is particularly difficult to study. If we consider that there are six WHO pre-qualified pentavalent vaccines, and three doses in a primary vaccine course, then there are 125 theoretically possible permutations of vaccine doses. The chances of any particular permutation having been studied are very low. As stated by Decker [10]: “once we are faced with multiple combination vaccines, the likelihood shrinks that any particular substitution will have been studied explicitly”. We studied only one of 8 possible permutations using the two vaccines, and it is unrealistic to assume that all 8 should be tested and more so that all 125 be tested. Halsey, in his 1995 paper entitled: “Practical considerations regarding the impact on immunization schedules of the introduction of new combined vaccines”, discussed the inherent problems related to the increasing number of combined childhood vaccines available and in turn, the increasing number of potential permutations. The evaluation of all potential permutations has to be balanced against the cost of running clinical trials. At the time he provided a conservative estimate on the cost of running one clinical trial to evaluate one possible permutation from all available combination vaccines at the time at between $100,000 and $300,000 [27]. If this is applied to all combinations of the pentavalent vaccines available on the current market, it equates to $12.5–37.5 million to evaluate all 125 permutations. Bearing in mind that this is an estimate based on 1995 figures, the cost in today’s market would likely be considerably in excess of this figure.

The WHO have stated that in principle the same wP-containing or aP-containing vaccine should be given throughout a primary course of vaccination and state that available data does not suggest that changing between an aP-containing and wP-containing vaccine interferes with safety or immunogenicity [5]. Thus, if the previous type of vaccine is unknown or unavailable, any wP vaccine or aP vaccine may be used for subsequent doses to complete a primary vaccination course started with either an aP or wP vaccine [5]. Our data support this, and show that changing from one wP vaccine to another after the first dose does not impact immunogenicity or safety.

In 2010, one of the available pentavalent vaccines at the time, Shan5, lost the WHO pre-qualification status. This created a shortage of pentavalent vaccines. In order to continue immunization programs that were underway, the WHO recommended, that for children who had begun but not completed an immunization schedule with Shan5, an alternative vaccine or vaccines be used to complete the schedule [28]. This is an example of a situation, in which pentavalent vaccines have been used interchangeably.

Despite the complexities of studying interchangeability, efforts should be made to study other available pentavalent vaccines in combination to increase the limited body of evidence on interchangeability in a primary vaccine course. This would benefit those making vital vaccine decisions in areas where vaccination is most needed.

5. Conclusions

Our results show that Quinvaxem can replace the second and third dose of a primary vaccination course started with Tritanrix HB + Hib without impacting immunogenicity or having any negative effect on safety and tolerability. Our findings provide scientific evidence supporting the interchangeability of Quinvaxem with other pentavalent vaccines, or components thereof.

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Conflicts of interest/disclosures: C. Jica, A. Macura-Biegun and M. Rauscher are employees of Crucell Switzerland AG. E. Alberto has no conflicts of interests to declare. M.R.Z. Capeding has received speaker honoraria, travel and research grants from Pfizer Inc., GlaxoSmithKline, Sanofi Pasteur and Novartis and a research grant from Crucell Switzerland AG for this clinical study. *Contributions:* C. Jica was involved in study design and analysis, and critically reviewed the manuscript. A. Macura-Biegun provided significant intellectual contribution and critically reviewed the manuscript. M. Rauscher was involved in analysis of safety data, manuscript writing, and critically reviewed the manuscript. M.R.Z. Capeding was the principal investigator and E. Alberto co-investigator, and both were involved in data collection, manuscript writing and critical review. All authors approved the final version of the manuscript. *Role of the funding source:* Crucell Switzerland AG was involved in study design, analysis and interpretation of data, writing of the report and in the decision to submit the article for publication.

References

[1] World Health Organization. Global Immunization Vision and Strategy (GIVS) 2006–2015. Available at: http://whqlibdoc.who.int/hq/2005/WHO_IVB_05.05.pdf [accessed 14.05.13].
[2] World Health Organization. Global Immunization Vision and Strategy. Progress report and strategic direction for the Decade of Vaccines. Available at: http://apps.who.int/gb/ebwha/pdf_files/WHA64/A64_14-en.pdf [accessed 05.06.13].
[3] Schmid DA, Macura-Biegun A, Rauscher M. Development and introduction of a ready-to-use pediatric pentavalent vaccine to meet and sustain the needs of developing countries – Quinvaxem (R): the first 5 years. Vaccine 2012;30:6241–8.
[4] World Health Organisation, UNICEF. Immunization Summary. Available at: http://www.childinfo.org/files/immunization_summary_2012_en.pdf [accessed 05.06.13].
[5] World Health Organization. Pertussis vaccines: WHO position paper. Wkly Epidemiol Rec 2010;85:385–400.
[6] UNICEF. Immunization. Available at: http://www.unicef.org/immunization/index_2819.html [accessed 05.06.13].
[7] UNICEF. Supplies and Logistics. Available at: http://www.unicef.org/supply/ [accessed 05.06.13].

[8] World Health Organisation. WHO Prequalified Vaccines. Available at: http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html [accessed 05.06.13].
[9] UNICEF. Contact Awards. Available at: http://www.unicef.org/videoaudio/PDFs/contract_awards_April_2012.pdf [accessed 19.12.12].
[10] Decker MD. Principles of pediatric combination vaccines and practical issues related to use in clinical practice. Pediatr Infect Dis J 2001;20:S10–8.
[11] Feldman S. Interchangeability of vaccines. Pediatr Infect Dis J 2001;20:S23–9.
[12] Greenberg DP, Feldman S. Vaccine interchangeability. Clin Pediatr (Phila) 2003;42:93–9.
[13] Suarez E, Asturias EJ, Hilbert AK, Herzog C, Aeberhard U, Spyr C. A fully liquid DTPw–HepB–Hib combination vaccine for booster vaccination of toddlers in El Salvador. Rev Panam Salud Publica 2010;27:117–24.
[14] Gatchalian SR, Ramakrishnan G, Bock HL, Lefevre I, Jacquet JM. Immunogenicity, reactogenicity and safety of three-dose primary and booster vaccination with combined diphtheria–tetanus–whole-cell pertussis–hepatitis B-reduced antigen content *Haemophilus influenzae* type b vaccine in Filipino children. Hum Vaccin 2010;6:664–72.
[15] Espinoza F, Tregnaghi M, Gentile A, Abarca K, Casellas J, Collard A, et al. Primary and booster vaccination in Latin American children with a DTPw–HBV/Hib combination: a randomized controlled trial. BMC Infect Dis 2010;10:297.
[16] UNICEF. Elimination of Maternal and Neonatal Tetanus. Available at: http://www.unicef.org/health/index_43509.html [accessed 06.06.13].
[17] World Health Organization. WHO Vaccine-Preventable Diseases: Monitoring System – The Philippines. Available at: http://apps.who.int/immunization_monitoring/globalsummary/countries?countrycriteria%5Bcountry%5D%5B%5D=PHL [accessed 06.06.13].
[18] Ortega-Barria E, Kanra G, Leroux G, Bravo L, Safary A, Lefevre I. The immunogenicity and reactogenicity of DTPw–HBV/Hib 2.5 combination vaccine: results from four phase III multicenter trials across three continents. Vaccine 2007;25:8432–40.
[19] Anderson EL, Decker MD, Englund JA, Edwards KM, Anderson P, McInnes P, et al. Interchangeability of conjugated *Haemophilus influenzae* type b vaccines in infants. J Am Med Assoc 1995;273:849–53.
[20] Scheifele D, Law B, Mitchell L, Ochnio J. Study of booster doses of two *Haemophilus influenzae* type b conjugate vaccines including their interchangeability. Vaccine 1996;14:1399–406.
[21] Greenberg DP, Pickering LK, Senders SD, Bissey JD, Howard RA, Blatter MM, et al. Interchangeability of 2 diphtheria–tetanus–acellular pertussis vaccines in infancy. Pediatrics 2002;109:666–72.
[22] Halperin SA, Tapiero B, Law B, Diaz-Mitoma F, Duval B, Langley JM, et al. Interchangeability of two diphtheria and tetanus toxoids, acellular pertussis, inactivated poliovirus, *Haemophilus influenzae* type b conjugate vaccines as a fourth dose in 15–20-month-old toddlers. Vaccine 2006;24:4017–23.
[23] Kwak GY, Kwon HJ, Kim JH, Kim HM, Park JS, Ma SH, et al. The immunogenicity and safety of DTaP interchangeable immunization among Korean children. Vaccine 2012;30:4644–7.
[24] Langley JM, Halperin SA, Rubin E, White C, McNeil S, Mutch J, et al. Safety and immunogenicity of 2 mixed primary infant immunization schedules of pentavalent diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, and *Haemophilus influenzae* type B vaccines at 2, 4, and 6 months of age: a randomized controlled trial. Pediatr Infect Dis J 2012;31:189–92.
[25] Centers for Disease Control and Prevention. General Recommendations on Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep;60:1–61.
[26] Public Health Agency of Canada. National Advisory Committee on Immunization. Canadian Immunization Guide: Seventh Edition – 2006. Principles of Vaccine Interchangeability. Available at: http://www.phac-aspc.gc.ca/publicat/cig-gci/ [accessed 05.06.13].
[27] Halsey NA. Practical considerations regarding the impact on immunization schedules of the introduction of new combined vaccines. Ann N Y Acad Sci 1995;754:250–4.
[28] World Health Organization. Shan5 vaccine delisted from WHO prequalification. Available at: http://www.who.int/immunization_standards/vaccine_quality/shan5_who_statement_27july10.pdf [accessed 25.05.13].